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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/481,733	01/11/2000	PATRICK V. WARREN	DIVER1240-5	6043

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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/481,733	WARREN ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply.

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 17-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,13,14 and 17-39* is/are rejected.

7)☒ Claim(s) *4-12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 2/28/03 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 28, 2003 has been entered.

The AF amendment filed July 22, 2002 amending the specification to correct clerical error, amending claims 1, 17, 27 and 33 and adding claims 36 and 37 has been entered.

The entry of said amendment was made to avoid renumbering of claims 36-39. According to CFR § 1.126, the added claims must be numbered by the applicant consecutively beginning with the number next following the highest numbered claim previously presented (whether entered or not).

The amendment filed February 28, 2003 introducing, relative to the AF amendment, amendments to claims 17 and 36 and addition of claims 38 and 39 has been entered.

Claims 1-14 and 17-39 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 13, 14, 17-24 and 35-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 13 and 14 are drawn to a polynucleotide encoding an aminotransferase with any donor-acceptor specificity having an amino acid sequence which is at least 70% identical to SEQ ID NOs: 25-32.

The term "aminotransferase" encompasses diverse class of enzymes having different substrate and stereo specificity with regard to the amino group donor and acceptor. While enzymes having amino acid sequences of SEQ ID NOs: 25-32 are aminotransferases or transaminases with a known specificity, it is unknown what specificity will have an aminotransferase having an amino acid sequence that is at least 70% identical to said sequences.

The putative activity of enzymes having the amino acid sequences of SEQ ID NOs:25-32 is based on the homology with other enzymes (pages 4-5; pages 7-8, Table

1). This homology is on average about 40%. An enzyme with 70% identity will have less than 30% homology to the known sequence. The enzymes to which SEQ ID NOs: 25-32 are homologous may have different donor-acceptor and stereo specificity. The correlation between the structure and the specific aminotransferase function is not disclosed in the specification nor is known in the art. Therefore, it is unpredictable what will be the specific aminotransferase function of a protein having an amino acid sequence that is at least 70% homologous to SEQ ID NOs: 25-32. The specification does not disclose identifying characteristics which would allow to distinguish an aminotransferase of a defined donor-acceptor and stereo specificity from another aminotransferase specific for a different donor-acceptor pair.

Thus, a DNA encoding an aminotransferase of an unknown specificity towards donor and acceptor of the amino group and having an amino acid sequence which is at least 70% identical to SEQ ID NOs 25-32 lacks sufficient written description.

Claims 17-24 and 35 are drawn to a probe comprising 10-50 nucleotides that has a region of nucleotides that is at least 70%, 90% or 95% identical to a target region of a DNA encoding any one of SEQ ID NOs: 25-32 which will hybridize to a polynucleotide that encodes any one of SEQ ID NOs:25-32 under very low stringency (or possibly even non-stringent) conditions of 0.9 M NaCl, 5.0 mM NaH_2PO_4, 5.0 mM Na_2EDTA, 0.5% SDS, 10X Denhardt's and 0.5 mg/mL polyriboadenylic acid at 45°C. Claims 36-39 are directed to a genus of nucleic acid probes which will hybridize to a

polynucleotide that encodes any one of SEQ ID NOs:25-32 under the above conditions. Thus, the claims are drawn to a probe of any structure.

The specification does not contain any disclosure of the structure and function of all nucleic acids which will hybridize to a region or entire polynucleotide encoding any one of SEQ ID NOs: 25-32 under conditions of 0.9 M NaCl, 5.0 mM NaH_2PO_4, 5.0 mM Na_2EDTA, 0.5% SDS, 10X Denhardt's and 0.5 mg/mL polyriboadenylic acid at 45°C. As these conditions are very low stringency at best (an possibly even non-stringent), the genus of nucleic acids that comprise these above probes is a large variable genus with the potentiality of having many different structures, encoding many different proteins and detecting a wide variety of target molecules with little or no similarity of structure or function. Therefore, many structurally and functionally unrelated nucleic acids are encompassed within the scope of these claims. The specification discloses only a single species within the genus i.e., a polynucleotide encoding any one of SEQ ID NOs:25-32 which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 1-3, 13, 14, 17-32 and 34-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide encoding a specific aminotransferase having an amino acid sequence as set forth in any one of SEQ ID NOs: 25-32 and a fragment thereof of 10-50 nucleotides, does not reasonably provide enablement for a polynucleotide encoding a specific transaminase or aminotransferase of an undefined specificity having an amino acid sequence at least 70% identical to any one of SEQ ID NOs: 25-32 and a probe of 10-50 nucleotides that hybridize under the requisite conditions to a polynucleotide encoding any one of SEQ ID NOs: 25-32. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7)considered in determining whether undue experimentation is required, are summarized the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-3, 13 and 14 are drawn to a DNA encoding an aminotransferase with any specificity in regard to the amino group donor and acceptor. Despite knowledge in the art to produce mutations in proteins and the isolation of DNA molecules, the specification fails to provide guidance as to where, and what type of (i.e., what amino acid to substitute into, add to and/or delete from the known sequence), changes in amino acid residues will result in an unspecified aminotransferase activity. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The state of the art does not allow the predictability of the properties based on the structure. The amino acid sequence of a protein determines its structural and functional properties and knowledge of which residues can be altered or removed, so that they retain 70% identity, and result in an unspecified aminotransferase activity is well outside the realm of routine experimentation. Since the state of the art does not allow the predictability of the properties based on the structure, it is unpredictable what will be the function, donor, acceptor and stereo specificity of an aminotransferase with the amino acid sequence 70% identical to SEQ ID NOs:25-32.

Claims 25-32 and 34 are drawn to a polynucleotide encoding an aminotransferase of a defined donor-acceptor specificity having at least 70% identical to a sequence selected from the group consisting of SEQ ID NOs: 25-32. The putative activity of enzymes having the amino acid sequences of SEQ ID NOs:25-32 is based on the homology with other enzymes (pages 4-5; pages 7-8, Table 1). This homology is

on average about 40%. An enzyme with 70% identity will have less than 30% homology to the known sequence. The state of the art allows, in most cases, to make DNAs encoding proteins with the same activity having about 95% identity.The specification does not support the broad scope of the claims which encompass all modifications and fragments of any sequence that is at least 70% identical to any one of SEQ ID NOs: 25-32 because the specification does **not** establish: (a) regions of the protein structure which may be modified without effecting each specific aminotransferase activity of each polypeptide of SEQ ID NOs: 25-32 of the instant invention; (B) the general tolerance of said polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining each requisite aminotransferase function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Claims 17-24 and 35-39 are so broad as to encompass any nucleic acid probe comprising or consisting of a sequence that hybridizes to a nucleic acid encoding any one of SEQ ID NOs: 25-32 under hybridization conditions of 0.9 M NaCl, 5.0 mM NaH_2PO_4, 5.0 mM Na_2EDTA, 0.5% SDS, 10X Denhardt's and 0.5 mg/mL polyriboadenylic acid at 45°C. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of nucleic acid probes. Since the nucleotide sequence of a probe determines its

structural and functional properties, predictability of which variants of a known sequence can be used as a probe for other target sequences requires a knowledge of and guidance with regard to the ways in which the probes' structure relates to the desired function. However, in this case the disclosure is limited to the structure and function of SEQ ID NOs:17-24 which encode SEQ ID NOs: 25-32, respectively.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a probe's sequence where modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any probe and the result of such modifications is unpredictable. Furthermore, the usefulness of any variant of a gene as a probe depends of the specificity of the probe for the target and the ability to exclude non-target nucleic acids from reacting therewith. In the instant case the scope of variants encompassed in the claimed probes is so broad that the vast majority of claimed probes within the scope of the claims could not be used as taught as either probes for the nucleic acids of SEQ ID NOs:17-24 nor for the isolation of other nucleic acids related to these nucleic acids as they would also cross react with an enormous number of unrelated nucleic acids under the very low stringency conditions recited in the claim. The specification fails to provide guidance for the selection of useful probes within the scope of the claims beyond guiding one to specific fragments of SEQ ID NOs:17-24.

However, the scope of claimed probes is vastly broader with little or no expectation of successful use thereof provided by the specification.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a DNA encoding an amino acid sequence at least 70% identical to SEQ ID NOs: 25-32 and having any or defined aminotransferase activity as well as any nucleic acid probe comprising or consisting of a sequence that hybridizes to a nucleic acid encoding any one of SEQ ID NOs: 25-32 under hybridization conditions of 0.9 M NaCl, 5.0 mM NaH_2PO_4, 5.0 mM Na_2EDTA, 0.5% SDS, 10X Denhardt's and 0.5 mg/mL polyriboadenylic acid at 45°C. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of probes having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 13, 14, 17-24 and 33-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, with dependent claims 2, 3, 13 and 14, and claim 33 are directed to a DNA encoding an enzyme with aminotransferase activity. The scope of the term "an enzyme with aminotransferase activity" is unascertainable because it is unclear what are enzymes other than aminotransferases that are included in the scope of the claim.

Claim 17, with dependent claims 18-24 and 35, is drawn to a probe of at least 10 to about 50 nucleotides having a region of nucleotides that is at least 70% complementary to a nucleotide. The length of "a region" is not defined. Therefore, the percent homology of the entire probe is undefined rendering the metes and bounds of the claim unascertainable.

Claims 17, 36 and 37 (upon which Claims 18-24, 35, 38 and 39 depend) are confusing in the recitation of "nucleic acid probe **comprising** a nucleic acid sequence **consisting** of...". The use of both open and closed language within the claim is confusing as to the scope of what is included. It is suggested that if applicants intent is to fully delineate the scope of nucleic acid components of the probe yet still allow any type of additional detectable label, that applicants recite "A nucleic acid probe consisting of a nucleic acid sequence and optionally a detectable label, wherein said sequence consists of...".

Claim 34 is unclear as reciting "the same amino group acceptor and donor" (emphasis added), wherein the amino group acceptor and donor are not defined.

Allowable Subject Matter

Claims 4-12 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Response to Arguments

Applicant's arguments filed February 28, 2003 have been fully considered but they are not persuasive.

Applicants argue the written description and enablement of claim 17 only. Applicants argue that the rejections are overcome because "amended claim 17 is directed to probes that hybridize to polynucleotides that encode a polypeptide that must have aminotransferase activity" (Remarks, page 6). This not persuasive because claim 17 does not contain the limitation that a polypeptide must have aminotransferase activity. Furthermore, limitation to undefined aminotransferase activity would be insufficient to preclude the 112, 1st paragraph, rejections in view of the discussions, *supra*.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

May 16, 2003